α-L-iduronidase therapy for mucopolysaccharidosis type I

Jakub Tolar
Paul J Orchard

Division of Hematology, Oncology, Blood and Marrow Transplantation, Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA

Abstract: More than 500 patients with mucopolysaccharidosis type IH (MPS IH; Hurler syndrome) have been treated with hematopoietic cell transplantation (HCT) throughout the world since the introduction of transplantation as therapy almost 30 years ago. More recently, the availability of recombinant α-L-iduronidase (IDUA) has resulted in the widespread treatment of less severe forms of MPS I with enzyme replacement therapy (ERT). In addition, over 50 MPS IH patients have been treated with a combination of ERT and HCT. The rationale for both ERT and HCT stems from the pivotal experiments performed 4 decades ago that showed α-L-iduronidase supplied in the environment can correct the accumulation of substrate in MPS I cells. Our purpose is to address the multiple applications associated with the therapeutic delivery of IDUA: intermittent delivery of recombinant protein (ERT), continuous administration through cellular therapy (HCT), the use of other stem cells or, potentially, correction of the enzyme defect itself through gene therapy approaches. Even though gene therapy and non-hematopoietic stem cell approaches, have yet to be tested in a clinical setting, it is possible that all these approaches will in the near future be a part of a paradigm shift from unimodal to multimodal therapy for MPS I.

Keywords: mucopolysaccharidosis type I, Hurler syndrome, hematopoietic cell transplantation, enzyme replacement therapy, co-modality therapy

Enzyme replacement therapy

Mucopolysaccharidoses are autosomal recessive disorders characterized by deficiencies of lysosomal hydrolases needed for the step-wise catabolism of complex carbohydrates termed glycosaminoglycans (GAG) (Neufeld 1991). For each disease, the specific enzyme deficiency defines which substrates accumulate, and the tissues which are primarily affected. In mucopolysaccharidosis type I (MPS I), the deficiency in α-L-iduronidase (IDUA) results in lysosomal accumulation of GAG heparan and dermatan sulfate (Bach et al 1972). Abnormal accumulation of these GAG leads to progressive cellular and multi-organ dysfunction.

The clinical phenotype of children with severe (ie, complete) deficiency of IDUA may be apparent at birth, but in the majority of cases these initial symptoms and signs may not be evident until at 6 to 8 months of age, and the diagnosis may not be made until some months later. Typically, the clinical findings may include hepatosplenomegaly, umbilical or inguinal hernia, evidence of cardiac disease (coronary artery disease or valvular abnormalities), obstructive airway disease, corneal clouding and retinal degeneration, chronic rhinitis and otitis, hydrocephalus, progressive neurocognitive deterioration, and multiple musculoskeletal abnormalities. Without treatment, early death is observed, usually between 5 and 10 years of age (Neufeld 1991; Orchard et al 2007).

In addition to patients with severe MPS I described above, two other clinical syndromes exist that are characterized by less severe deficiencies of IDUA; Hurler-Scheie

Correspondence: Jakub Tolar
Division of Pediatric Hematology, Oncology, Blood and Marrow Transplantation MMC 366,
420 Delaware Street SE, Minneapolis, MN 55455, USA
Tel +1 612 626 5501
Fax +1 612 624 3913
Email tolar003@umn.edu

syndrome with an intermediate phenotype and Scheie syndrome with a mild phenotype. In contrast to patients with Hurler syndrome, the patients with Hurler-Scheie and Scheie syndromes have mild or no cognitive impairment. While generally the signs and symptoms of these more attenuated disorders occur later and are less severe than in patients affected with Hurler syndrome, significant medical problems may be seen paralleling what is seen in the Hurler patients.

While traditionally labeled as three distinct entities, Hurler (frequency 1:100,000 live births), Hurler-Scheie (1:115,000 live births), and Scheie (1:500,000 live births) syndromes represent a progressive clinical continuum, with the three phenotypes not necessarily clearly delineated (Roubicek et al 1985; Scott et al 1995; Meikle et al 1999). This reflects the substantial heterogeneity in the genotypes encountered in the IDUA gene, and may reflect other modifying genes affecting the severity of disease (Pastores et al 2007).

The IDUA gene is localized to chromosomal band 4p16.3. The total length of the gene is 19 kilobases and includes 14 exons. In wild type form, it codes for 653 amino acids and leads to the production of a 82 kDa protein (Schuchman et al 1984; Unger et al 1994). Many IDUA mutations are private but some exhibit a significant bias in different populations (Lee-Chen et al 1999; Lee-Chen and Wang 1997; Rempel et al 2005). For example, approximately 70% of patients with European ancestry carry one of the two severe mutations, W402X or Q70X, yet the spectrum of the MPS I syndromes presents a significant challenge in defining treatment (Scott et al 1992, 1993; Sugawara et al 2008).

Since the 1980s HCT has proven to be a life-saving measure for the severe form of MPS IH (Hobbs et al 1981; Orchard et al 2007). The significant toxicities associated with HCT, however, have made its application in less severe forms (Hurler-Scheie and Scheie syndrome) difficult to justify.

The availability of recombinant IDUA (laronidase) for utilization as enzyme replacement therapy (ERT) has been a major advancement in the field. ERT has become a mainstay of therapy for patients with Hurler-Scheie and Scheie, the attenuated forms of IDUA deficiency that do not have central nervous system manifestations of their disease. As the intravenous administration of the enzyme has been shown to not effectively cross the blood brain barrier, the treatment of severe MPS I deficiency with enzyme replacement alone has not been accepted; in the Hurler population, HCT remains the standard of care. However, one major consequence of the success of ERT in MPS I has been the potential addition of ERT prior to transplantation in, patients with Hurler syndrome.

As a prerequisite for the human studies, the infusion of enzyme as therapy has been evaluated in animal models of MPS I (Kakkis et al 1996, 2001b; Clarke et al 1997; Ohmi et al 2003). Two murine models with genetically engineered IDUA deficiency, as well as feline and canine MPS I models, exist. Even though they are not full phenocopies of human disease, all mimic the human MPS I disorder biochemically (increased GAG levels in tissues and in urine) and in the development of visceral and central nervous system pathology. Studies in these animal models showed that both accumulation of GAG and GAG-mediated pathological features can be alleviated by treatment with systemic recombinant enzyme, and suggested that a benefit could be expected by ERT in humans (Shull et al 1994; Kakkis et al 1996, 2001b).

The recombinant IDUA, available for clinical use since 2001, is a polymorphic variant of the human enzyme produced by recombinant DNA technology in the Chinese hamster ovary cell line (Kakkis et al 1994). In the study that defined the ERT field, Kakkis et al (2001a) treated 10 patients from 5 to 22 years of age with MPS I with recombinant human IDUA at a dose of 125,000 units per kg of body weight given intravenously once weekly for 52 weeks. The authors concluded that the therapy reduced lysosomal storage of GAG and ameliorated some of the clinical manifestations of MPS I, with effects on growth, restrictions of range of motion at the shoulder and elbow, and sleep apnea. In addition, urinary GAG, a rough measure of total body GAG load, decreased after 3 to 4 weeks of IDUA treatment. Approximately half the patients had urticaria during IDUA infusion, but in general the ERT was tolerated well. Importantly, serum antibodies to IDUA were detected in 4 out of 10 patients, but this did not appear to affect the response to therapy (Kakkis et al 2001a). A follow-up study concluded that the patients continued to exhibit an improved ability to perform normal daily activities (Sifuentes et al 2007). As such, these data demonstrate in a compelling fashion an opportunity for long-term alteration of morbidity associated with the attenuated forms of MPS I.

Since that time, additional information has been provided in regards to the treatment of MPS I with enzyme therapy (Wraith 2001). Foremost among these is a placebo-controlled, randomized, double-blind study of Wraith et al (2004). Forty-five MPS I patients were evaluated, 22 of whom received 0.58 mg/kg (100 units/kg) of intravenous IDUA weekly for 26 weeks, and 23 of whom received a placebo. It was shown

that IDUA was well tolerated, and reduced urinary GAG. Critically, statistically significant improvement was documented in the ability to perform physical tasks and in the respiratory capacity in the IDUA-treated group compared to placebo-treated patients (Wraith et al 2004).

The same group has recently published a large, multinational, open-label study of 20 patients with MPS I who were less than 5 years old (Wraith et al 2007). Consistent with the previous report, ERT was again shown to be well tolerated, with a decrease in GAG storage (as evidenced by decreased hepatomegaly and GAG urinary clearance), and to provide clinical benefits such as improvement in sleep apnea and hypopnea to patients with severe MPS I in this early age group. Interestingly, a more robust decrease in GAG total body load was observed in patients who were receiving a higher dose of IDUA (200 units/kg vs 100 units/kg), and those with low anti-IDUA antibody levels.

These observations are relevant since IDUA therapy may be optimal at higher doses than those currently used. In addition, there is a suggestion that the immunologic response to the drug can be a formidable barrier to both ERT and HCT. Therefore, a central question in MPS I therapy is how completely IDUA will correct the deficiency in various organ systems, and how generation of anti-IDUA antibodies in immunocompetent hosts will impact the efficacy of serial, indeed life-long, IDUA infusions.

Intuitively, one would expect that IDUA naïve (ie, $IDUA^{null}$ MPS I/Hurler syndrome) recipients would develop an immune response to systemically infused enzyme. In fact, this has been observed in both animal and human recipients of recombinant enzyme (Kakkis et al 1996; Shull et al 1996; Turner et al 2000; Glaros et al 2002). In an effort to minimize the antibody response, induction of immune tolerance in canine MPS I model with a regimen consisting of cyclosporine and azathioprine has been tested and proven to be successful (Kakkis et al 2004a).

Even more relevant to human disease has been the study of Kakavanos et al (2003) who observed that the patients who had an IDUA-specific immune reaction initially, developed immune tolerance after 2 years of treatment with IDUA. As accumulating data indicate that almost all ERT-treated patients develop anti-IDUA antibodies, it is important to recognize that in the majority of cases IDUA-directed antibodies appear to be non-neutralizing, and as such would not be expected to affect the active site of the enzyme on which the beneficial effects of ERT depend.

Even though most available studies have demonstrated that ERT is generally safe and efficacious, ultimately the long-term impact of ERT is unknown (Coman et al 2008). This is in part because of immune responses that may prove important over long periods of enzyme administration. It is also because the effects of intermittent ERT on different tissues are likely to be heterogeneous in response to therapy (eg, brain, bone, and heart valves are likely to be more resistant to ERT), and because how these responses are maintained over years of therapy is unknown. Based on these limitations, plus the high cost of ERT, the need for weekly infusions over a lifetime, and the possibility of immune-based reactions that may complicate therapy, the critical question is: should cellular therapy be used alone or integrated as multimodal therapy with ERT to best provide optimal correction of IDUA deficiency?

Cellular therapy

The rationale for HCT originated from studies of Neufeld et al which showed that "cross correction" of $IDUA^{null}$ cells with externally supplied IDUA is possible (Fratantoni et al 1968a, b; Bach et al 1972; Neufeld 1991). IDUA secreted by donor cells is modified by the cellular mechanisms with the addition of mannose-6-phosphate residue. After secretion, glycosylated IDUA is taken up by recipient $IDUA^{null}$ cells via mannose-6-phosphate receptors present on the cellular and subcellular membranes of the recipient cells (Hasilik and Neufeld 1980). After internalization, the enzyme is channeled into lysosomes where it takes part in degradation of GAG (Fischer et al 1980). Therefore, as functional IDUA is provided by donor cells, HCT has the ability to provide the enzyme in a manner akin to ERT, except on a continuous rather than intermittent basis.

Allogeneic stem cell transplantation for MPS I was first performed by Hobbs et al and was quickly followed by others as a life-saving measure for children with severe MPS I (Hobbs et al 1981; Peters et al 1996, 1998a, 1998b; Vellodi et al 1997; Souillet et al 2003; Hansen et al 2008). Heterozygous to normal serum levels of IDUA are routinely achieved after HCT, and the progression of this debilitating disease is arrested in most, but not all, organ systems. Initially, only human leukocyte antigen (HLA) matched related donors were used in order to minimize the immune-related complications of HCT, specifically graft-versus-host disease (GVHD). However, as most affected children do not have an HLA-matched related donor, we and others have explored the potential of alternative donor transplantation using unrelated HLA-matched donors or cord blood grafts. Over the last 3 decades, conditioning regimens, HLA typing techniques and the ability to identify well matched stem cell grafts for HCT has been improved greatly, and HCT remains

the treatment method of choice for the severe form of MPS I (Staba et al 2004; Boelens et al 2007; Orchard et al 2007).

Several important concerns, however, remain. First, graft failure has been observed in as many as one third of MPS I patients treated with HCT (Grewal et al 2002). In a large recent European study of outcomes of HCT for Hurler syndrome, Boelens et al (2007) reported more graft failure with T-cell depletion and reduced intensity conditioning, and less graft failure when cord blood versus bone marrow has been used as a graft source. This is consistent with findings of Staba et al (2004) who reported favorable outcomes of MPS IH (MPS I Hurler syndrome) in recipients of cord blood HCT. Second, the conditioning regimen has been an important determinant of HCT-related complications, which include infection, immune injury such as GVHD, or direct injury to tissues such as the lung from chemotherapy and radiation. Furthermore, late effects after HCT include increased risks of cancer, sterility, effects on growth, and chronic GVHD.

Combination therapy

Unfortunately, some complications of HCT appear more common in MPS IH patients. In addition to graft failure discussed above, respiratory difficulties have been frequently observed, and many MPS IH children require mechanic ventilation in the peri-transplant period. These complications include lower respiratory infections, idiopathic pulmonary syndrome and, one of the most difficult complications to effectively treat, pulmonary hemorrhage (Gassas et al 2003; Tolar et al 2008). As the upper airway is typically compromised in MPS IH children due to GAG deposition in oral, nasal and laryngeal tissues, these patients may be at greater risk for intubation and prolonged ventilation, which in turn increases the risk of multiorgan failure and poor outcome of HCT.

Thus, we and others reasoned that ERT in peri-transplant period has a potential to decrease GAG accumulation in lung and other visceral tissues prior to transplantation, which in turn may decrease the risk of life-threatening complications during HCT in MPS IH patients (Tolar et al 2007; Cox-Brinkman et al 2006).

Among the first communications of this approach was a multi-institutional report of 12 MPS IH recipients of combined therapy (ERT and HCT) by Grewal et al (2005). The median duration of ERT was 12 weeks before HCT and 7 weeks after HCT. Eight patients had complete donor engraftment and 11 of 12 survived at a median time of follow-up of 3 months (1 child died of pulmonary hemorrhage). Based on these case studies, it was concluded that the ERT and HCT combination therapy is safe and feasible, but prospective studies were needed to further evaluate the outcomes of co-modality therapy (Grewal et al 2005).

The European study lead by Cox-Brinkman et al (2006) also observed that ERT with HCT has been well tolerated. Nineteen of 22 patients studied were surviving (2 patients died after HCT repeated for graft failure). The generation of anti-IDUA antibodies has not been correlated with development of graft failure, but overall no benefit of ERT for this population of patients could be documented. Thus, these authors concluded that only the patients in poor clinical condition would benefit from ERT before HCT.

Of note, the patient group described in this study was heterogeneous: patients came from multiple institutions, were recipients of various stem cell grafts (bone marrow, peripheral blood stem cells, cord blood, matched and mismatched family donors, and unrelated donors), were transplanted after variable conditioning regimens (4 different myeloablative regimens, 1 reduced intensity regimen), and received a varied number of stem cell grafts (approximately one third received second transplants and about 10% received a third HCT) (Cox-Brinkman et al 2006).

In light of this, we chose to investigate prospectively the combination of ERT and HCT, utilizing a single conditioning regimen, receiving a similar number of enzyme infusions, and providing consistent supportive care in a single transplant center (Tolar et al 2007). Seven patients were studied at a median age of 1.5 years at the time of myeloablative HCT. Before HCT, 5 had pulmonary complications (pneumonia with hospitalization, abnormal sleep study, reactive early disease, and oxygen needs), which would be expected to increase their risk of complex HCT-related complications significantly. The patients were treated with either cord blood transplants or related-donor bone marrow. All survived and their outcomes appeared superior to those of patients with similar number of pulmonary risk factors who were treated with HCT alone.

Importantly, we confirmed the findings of others who showed that anti-IDUA antibodies (which develop in most if not in all of the patients) did not appear to compromise donor engraftment. Theoretically, it is possible that pre-HCT clearance of GAG by ERT from bone marrow stroma could make the recipients' bone marrow niche a more permissive environment for the engraftment of donor cells. Therefore, we favor the interpretation that all patients with severe MPS I, regardless of their clinical condition prior to transplant, could benefit from combination therapy with

ERT and HCT, and this co-modality therapy is offered to all families undergoing transplantation for MPS IH at our institution (Tolar et al 2007).

Taken together, the cumulative data reflecting the results of ERT and HCT co-modality therapy indicate that it is a safe and effective regimen which is now gaining wide acceptance. Despite the apparent benefits of ERT + HCT therapy, however, little is known about its long-term efficacy. In addition, there are several obstacles that hinder the advancement of this approach. One is the high cost and the limited availability of ERT in some countries. The second relates to the degree of correction on a cellular level in various tissues achieved in a defined period of time prior to transplantation, and whether this can be correlated with long-term sustained benefits for the MPS IH patients. Thirdly and significantly, intravenously administered IDUA does not appear to have the capacity to penetrate several organ systems – most notably brain, bone, and the heart valves. In addition, it is unclear at present whether the additive benefit of ERT and HCT observed early after co-modality therapy will translate into improvement (over and above HCT itself) of mental, musculoskeletal and cardiac disabilities in MPS I patients now surviving long term.

Brain

The major obstacle to translocation of enzyme delivered intravenously across the blood-brain barrier could in theory be overcome by infusion of IDUA into the spinal canal or lateral ventricles of the brain. This approach has been modeled successfully in the canine model of MPS I (Kakkis et al 2004b, Dickson et al 2007). Based on the animal data, Dickson et al (Dr Dickson, pers comm, May 2008) are testing intermittent intrathecal ERT in patients with attenuated MPS I disease to treat progressive narrowing of cervical spinal canal. While promising, these therapies are still in the early stages and, because of the dynamics of spinal cord compression in MPS I (Kennedy et al 1973; Kaufman et al 1982), data documenting outcomes with intrathecal delivery will not be available for several years.

Even more importantly, data from canine MPS I model suggest that intrathecal ERT has the potential to treat central nervous system and mental decline in humans (Dickson et al 2007). Even though some treated animals developed meningeal inflammation, it is encouraging that with improved pharmaceutical formulation the side effects of intrathecal administration in patients were minimal (Dr. Dickson, pers comm, May 2008). The experience with intravenous ERT has shown that, for a beneficial effect, frequent administration is required; this would suggest that the effects of intermittently dosed intrathecal ERT will be also be transient, although the frequency of administration may be less than what is required via the intravenous route (Dickson et al 2007). This would of course pose difficulties for the life-long treatment of IDUA deficiency in the central nervous system.

It is plausible that intrathecal ERT will "bridge" the time between diagnosis and IDUA production by donor cells in the brain of the recipient following donor hematopoietic engraftment. The benefits of HCT in the brain appear to stem from the ability of the donor hematopoietic cells to migrate from systemic vessels to the brain parenchyma after HCT (Shapiro et al 1995; Kennedy and Abkowitz 1997; Peters et al 1998c; Krivit et al 1999). The cells implicated in this process are microglia, hematopoietic cells of monocytic lineage (Krivit et al 1995). The dynamics of this engraftment are not well understood, as it is difficult to determine in a clinical setting. However, several lines of evidence indicate that after HCT, donor microglia home to and engraft in the brain in sufficient numbers in both mice and humans to arrest the anticipated ongoing neurologic deterioration.

An alternative, "Trojan horse" approach to crossing the blood-brain barrier has been tested by Pardridge et al (2005a, b, c) who used fusion proteins to transport IDUA across blood-brain barrier via the endocytosis-exocytosis pathway. Similarly, we have chosen a transferrin-IDUA fusion gene product to provide a proof of the concept that transferrin receptor-mediated transcytosis across blood brain barrier endothelium can be used as a functionally efficient pathway for an uptake of IDUA in brain cells, including neurons (Osborn et al 2008).

Lastly, based on the assumption that microglial engraftment after HCT or intermittent IDUA intrathecal dosing both have sufficient drawbacks to make them alternative strategies worth exploring, continuous IDUA infusion into the spinal fluid by a semi-permanent pump within the central nervous system or externally by catheter delivery is theoretically feasible.

Bone

One of the most prevalent and difficult to manage long-term difficulties in otherwise successfully treated Hurler patients include musculoskeletal manifestations from progressive dysostosis multiplex (Oestreich 1985; Schmidt et al 1987; Masterson et al 1996; Odunusi et al 1999; Weisstein et al 2004). The patients exhibit numerous orthopedic complications despite HCT, including kyphosis, scoliosis, cervical

spine instability, genu valgum, and carpal tunnel syndrome. Despite full donor engraftment after "successful" HCT (Field et al 1994; Weisstein et al 2004; Khanna et al 2007; Taylor et al 2008; Polgreen et al 2008), many patients require multiple surgeries, and, as a result of the combined effect of the primary MPS I disease and the impact of the conditioning therapy on endocrine and bone functions, are affected with musculoskeletal limitations for the rest of their lives.

Heart

Cardiac pathology is prominent in patients with Hurler syndrome. While coronary artery disease and cardiomyopathy appear to be treated by successful HCT (and presumably ERT), heart valve abnormalities do not appear to be corrected by ERT or HCT, although it is possible that these interventions may affect progression of valvular disease (Renteria et al 1976; Vinallonga et al 1992; Dangel 1998; Braunlin et al 2003, 2006; Hirth et al 2007). Murine model of MPS I (Clarke et al 1997; Russell et al 1998; Ohmi et al 2003) represents a platform for testing various interventions including targeted cell therapy or attenuation of thickening of heart valves by secondary means such as decreasing the GAG-mediated inflammation (Taylor and Gallo 2006).

Gene therapy

Yet another source of investigations likely to be relevant in the future are data generated by gene therapy experimentation in animal models of MPS I (Lutzko et al 1999; Zheng et al 2003; Ellinwood et al 2004; Hartung et al 2004; Di Domenico et al 2005; Kobayashi et al 2005; Liu et al 2005; Ponder and Haskins 2007; Traas et al 2007; Chung et al 2007; Watson et al 2006; Ma et al 2007). Despite significant complications and side effects observed in the viral-mediated gene therapy clinical trials for X-linked severe combined immune deficiency and chronic granulomatous disease (Baum et al 2003; Hacein-Bey-Abina et al 2003a, b; McCormack et al 2003; Fischer et al 2004; von Kalle et al 2004), optimism remains that improved viral and non-viral vectors will prove to be effective for delivery of enzymes such as IDUA in a sufficiently high local concentration to alter the sites (eg, brain, bones, heart) that are not fully corrected by the currently available therapies. Aside from immune reactions to the viral proteins, most lethal complications of gene therapy trials were caused by disruption of gene integrity and regulation in the recipient. For this reason, tremendous amounts of research have focused on the mechanism and risk quantification of insertional mutagenesis. The probability of uncovering a relatively low-frequency/high-risk side effect event (such as the development of leukemias occurring in the X-linked severe combined immune deficiency trial) will be difficult in a surrogate organism due to the prolonged latency of these events. Alternatively, cancer-prone animals or cell-based assays are likely to be used to define risk-benefit ratio assessments prior to future viral-based clinical trials. Improved vector design, enabling for example gene insertion in a specific genome location, or insulation of the gene of interest from the rest of the genome, or gene correction by homologous recombination to avoid insertional mutagenesis, would represent important advances in gene therapy (Porteus et al 2006).

Stem cell gene therapy

The possibility of using gene therapy to correct hematopoietic cells of the recipient ex vivo followed by re-infusion with or without conditioning therapy, would avoid the substantial toxicity of allogenic transplantation, including GVHD, sustained immune suppression, and graft rejection. In addition, non-hematopoietic stem cells isolated from bone marrow can be corrected *ex vivo* and, because of their multi-lineage potential, could be harnessed for organ–specific delivery of IDUA-producing cells. It is of interest that donor mesenchymal stem cells (MSC) can home to sites of tissue injury (Kunter et al 2006; Prockop 2007). MSC have been shown to be safe in the first clinical trials for treatment for GVHD (Le Blanc et al 2004; Aggarwal and Pittenger 2005; Le Blanc and Ringden 2005a, b; Prockop and Olson 2007).

The options for non-hematopoietic stem cells in therapy of MPS I are multiple (Muller et al 2006). First, allogenic MSC have been used in metachromatic leukodystrophy and appeared to improve nerve conduction velocities in several patients (Koc et al 2002). Therefore, they can perhaps be used as a "depot" of cells able to produce the IDUA continuously and potentially at sites other than those targeted by hematopoietic cells. Second, allogenic or gene-corrected autologous MSC can be considered as treatment of neurologic, bone, and heart valve disease not readily accessible by freely diffusible IDUA after HCT. In theory, they could be infused intravenously (to correct visceral GAG storage) or intrathecally (to correct brain pathology). Lastly, when used at the time of hematopoietic cell infusion, MSC have a potential to improve engraftment as well as a potential to prevent acute GVHD, as has been shown already in patients with malignant disorders receiving HCT.

Summary

Multiple agents and interventions are the mainstay of therapy for malignancies and infectious disease, and clearly seem

to be the future trend in treatment of enzymopathies such as MPS I as well. As detailed above, the multiple tools available to us today for IDUA delivery include delivery of protein systemically and intermittently by ERT. Alternatively, enzyme may be delivered by a cellular approach using either allogenic cells producing enzyme such as HCT, or by gene therapy vectors to correct IDUA deficient cells, or to overexpress the gene product. These strategies will be available to researchers and clinicians interested in defining more efficacious and less toxic therapy for MPS I patients in the future.

We believe that the best available approach for newly diagnosed MPS IH patients at the current time is combination therapy of ERT and HCT. The use of ERT can prepare the patient for the transplant process by decreasing the GAG burden in the viscera, thereby providing an opportunity to limit the significant toxic effects of HCT. This is of key importance since MPS IH patients with pulmonary disease are at higher risk for HCT complication than MPS IH children without pulmonary symptoms before HCT (unpublished data).

This pre-emptive attempt to decrease morbidity associated with HCT by using ERT needs to be defined better by prospective long-term and short-term quantitative metrics, such as urinary GAG, determination of organomegaly, evidence of airway obstruction, and neuropsychological evaluations. Organized, multi-institutional efforts spanning experiences and practices throughout the world will provide a unified collection of data and evidence-based approaches, allowing conclusions to be drawn more expediently as greater numbers of patients can be evaluated (Pastores et al 2007). For rare disorders such as MPS I, collaborative studies will be important in moving the field forward and achieving optimal outcomes for these patients and their families.

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Disclosures

The authors report no conflicts of interest.

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